STUDIES OF THE ORTHO-POSITRONIUM LIFETIME FOR CANCER DIAGNOSTICS*

Z. Bura[a,†], K. Dulski[a], E. Kubicz[a], P. Małczak[b], M. Pędziwiatr[b]
M. Szczepanek[c], E.Ł. Stępień[c], P. Moskal[a]

[a]Department of Experimental Particle Physics and Applications
Institute of Physics, Jagiellonian University
Łojasiewicza 11, 30-348 Kraków, Poland
[b]2nd Department of General Surgery, Jagiellonian University Medical College
Kopernika 21, 30-348 Kraków, Poland
[c]Department of Medical Physics, Institute of Physics, Jagiellonian University
Łojasiewicza 11, 30-348 Kraków, Poland

(Received December 9, 2019)

Positron Annihilation Lifetime Spectroscopy (PALS) is a technique based on the analysis of the lifetime of positronium emitted from implanted or delivered positronium donors. This technique employs the lifetime and intensity dependence on the structure of analyzed material. Due to this specific features, PALS might be used in further research protocols and clinical studies for cancer diagnostic purposes. This article reports the progress in the study design, main objectives of the study, protocols of measurements and data analysis and further perspective of this study. The main goal of this work was to show the effectiveness of this method and progress in its development. For this purpose, colorectal cancer was examined.

DOI:10.5506/APhysPolB.51.377

1. Introduction

Nowadays cancer is a major cause of mortality and it affects people all around the world. Among many, the colorectal tumor is the third and second most common source of cancer among men and women, respectively [1]. Understanding of cancer biology is critical to develop a rationally designed therapy and to offer preventive options [1]. One of the biggest challenges of diagnostic medicine is early recognition of the disease and precise localization

* Presented at the 3rd Jagiellonian Symposium on Fundamental and Applied Subatomic Physics, Kraków, Poland, June 23–28, 2019.

† Corresponding author: zuzanna.bura@student.uj.edu.pl

of its cause [2, 3]. Combining the J-PET tomography [4–8] (that enables detection of cancer at the early stage of its development) with Positron Annihilation Lifetime Spectroscopy (which can test structural changes in biological polymeric systems), it may be possible to tell more about the structure of the cancer without a biopsy [2, 8, 9]. In this article, the basics of these measurements are explained. This research will allow to establish the precision of J-PET tomograph for PALS measurements [6]. Samples of both colon normal and cancer tissues are studied *ex vivo* by means of the PALS detectors.

2. Method

The main objective of this study is the investigation of differences in life-times of ortho-positronium (o-Ps) formed in samples obtained from colon cancer and normal tissues. We assume that positron emitted from ^{22}Na thermalizes in cancer or normal tissue and forms a positronium whose lifetime is different and depends on tissue structure and metabolism. The source of positrons is a β^+ radioactive isotope which decays to an excited nucleus which, subsequently, deexcites via emission of the gamma quantum. For example, ^{22}Na isotope after emission of a positron transforms into the excited ^{22}Ne nucleus which then emits almost immediately (on the average in about 3 ps) γ quantum with the energy of 1274 keV [6, 10]. The positron emitted into the sample thermalizes and forms a positronium atom or annihilates directly with one of the electrons from the sample. Positronium, depending on the spin state, can annihilate with emission of two or more γ quanta. Para-positronium (p-Ps) state ($S = 0$) annihilates with emission of two γ quanta with mean lifetime of 0.125 ns in vacuum, while o-Ps ($S = 1$) annihilates with emission of three γ quanta with a mean lifetime of 142 ns in vacuum [11]. However, due to a processes such as, for example, pick-off or ortho–para conversion, there is a chance that o-Ps annihilates with emission of two γ quanta and a significantly lower mean lifetime [11]. The latter depends on the size of the space between molecules, so-called "free volumes". The smaller a free volume is, the lower is the mean lifetime of o-Ps [12–14]. Changes of the o-Ps mean lifetime reflect changes in the material structure and, therefore, they may be connected to the morphology of cells of the living organisms [2, 5, 9, 10, 15]. Taking into consideration that o-Ps lifetime modifications result from electromagnetic interactions of o-Ps with water molecules and other cell-building compounds as proteins or lipids, properties of positronium, for example, the lifetime, may be different in cancerous and normal tissues due to their different molecular structure.

3. Colon cancer

Carcinogenesis of colorectal cancer is not completely understood. The reason of this process is the formation of multiple cytogenetic and epigenetic changes as a result of long exposure to environmental and innate cancer risk factors that disrupt cellular homeostasis [16]. These environmental factors may be, for example: wrong diet, smoking or diabetes. The gene responsible for colorectal cancer is the adenomatous polyposis coli (APC). Germ-line mutations in the APC gene result in familial adenomatous polyposis (FAP), one of the principal hereditary predispositions to colorectal cancer [3]. Colon cancer is one of the most common cancer types in the world. The risk of geting colorectal cancer rises dramatically with age, by the age of 70, approximately half of the modern people will have developed adenoma [1, 3]. At least four changes in genome sequences need to take place in order to cause the colorectal cancer evolution. The main targets of the changes are: KRAS (oncogene), APC, SMAD4 and TP53 (tumour suppressor genes) [3]. Macroscopically, tumors have various morphological forms. Ascending colon tumors can occur with an exophytic/fungal growth pattern with the formation of a large polypous mass, often with ulceration. In the descending colon, tumors tend to have a flat, annular growth leading to narrowing of the intestinal lumen [3]. Colonoscopy is the basic examination enabling the diagnosis of colorectal cancer [1]. This method is one of the endoscopic examinations that could provide the visual image thanks to a CCD camera or a fiber optic camera on a flexible tube passed through the anus. About 1 out of 200 people who undergo colonoscopy experience a serious complication, for example, gastrointestinal perforation or bleeding [17]. In this case, the scientists from the Institute of Physics of the Jagiellonian University developed another method of diagnostic colon cancer. Combining PET scanner with PALS technique [6] may improve a colon cancer diagnostic with less complications, as it will be an non-invasive examination.

4. Measurements

Samples were delivered from the 2nd Department of General Surgery, Jagiellonian University Medical College in Kraków. Both normal and cancerous tissues originated from the large intestine. For the studies, all patients with colrectal cancer were accepted, the only excluding criteria were: the size of tumor (if smaller than $\sim 1\,\mathrm{cm}^3$) and positive tests for HIV, hepatitis B and C. Reaserch has been conducted based on the agreement of the Bioethical Committee of the Jagiellonian University No. 1072.6120.13.2019. During the surgery, half of the tumor was allocated for histopathology examination while the other part was transferred to the Faculty of Physic, Astronomy and Applied Computer Science for PALS measurements. The tissue samples

were transported in the thermally-isolated container, to maintain a stable temperature through all procedures. Epidemiological and clinical data regarding risk factors, treatments and patient conditions and co-morbidities were collected. Additionally, data related to cancer stage and progression were collected and confirmed by histopathological examinations. Patients with radio- and chemotherapy prior to surgery were included in the study to test the influence of different treatments on o-Ps lifetime.

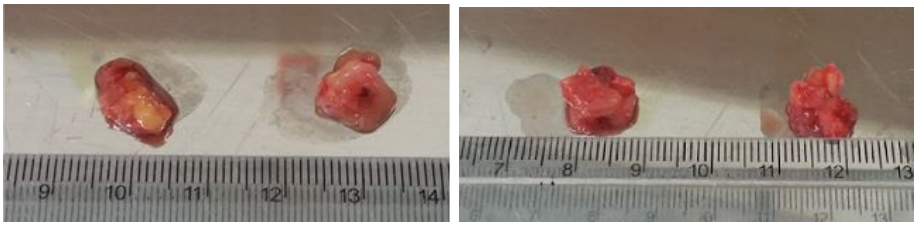

Fig. 1. Examples of normal (left) and cancerous (right) samples of colon tissues studied with PALS.

Both, the colon cancer and normal tissue samples were placed in an aluminium chamber. THe ^{22}Na source (1MBq) was used as a positron emitter placed in between two parts of the same tissue. The chamber was inserted between two BaF_2 scintillators as shown in Fig. 2. The two detectors were red out by the DRS4 digitizer.

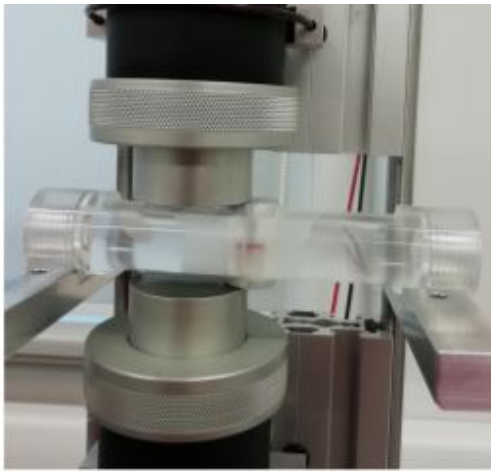

Fig. 2. Photograph showing the experimental setup used in performed PALS measurements. Two scintillator detectors with BaF_2 crystals were used. The sample was encapsulated together with an ^{22}Na source sealed in 0.6 μm thick Kapton foil in the aluminum chamber seen in the picture.

As a result of the measurements, we have obtained for each sample a PAL spectrum which was then used to estimate the mean lifetime in the studied tissues. The analysis was performed by the PALS Avalanche software [18, 19]. In Fig. 3, one can see exemplary PAL spectrum with fitted model. Each component is related to the different type of positron annihilation.

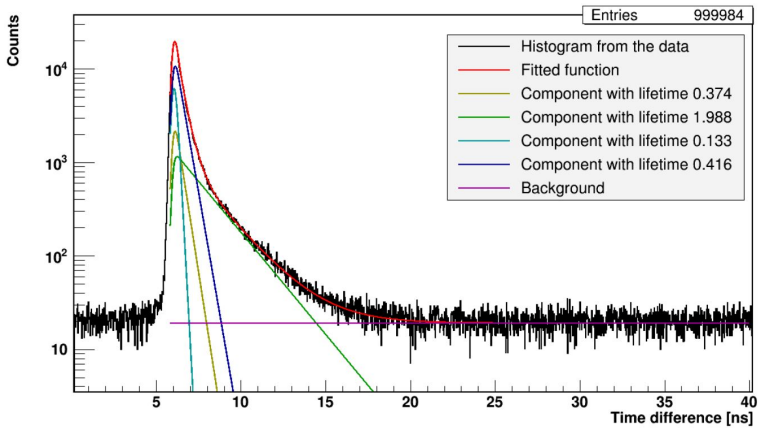

Fig. 3. (Color online) Exemplary PAL spectrum for a cancer sample from patient No. 1. Red curve indicates model fitted to the positron lifetime distribution. It consists of a contribution originated from the detection setup itself (due to its time resolution) constant background (purple) and a set of exponential functions originating from positron annihilation: o-Ps decay (green, with lifetime 1.988 ns), free positron annihilation (blue, with lifetime 0.416), annihilation in the source itself (olive green, with lifetime 0.374) and p-Ps decay (light blue, with lifetime 0.133).

5. Conclusions

The mean o-Ps lifetime can be successfully estimated for every sample, both normal and cancer. A detailed procedure for sample preparation and measurement was developed and tested for performing repeatable measurements. Influence of aforementioned risk factors on the structural alterations was tested in correlation with o-Ps mean lifetime. The most challenging aspect of conducted research is to determine how the macroscopic factors mentioned above affect changes at the atomic level. The main difficulty is to find a diagnostic relevance pattern between the o-Ps lifetime and different biological processes occurring within cells and tissues which changes not only its structure but also cellular signaling and activity.

This work was supported by the Foundation for Polish Science through the TEAM/2017-4/39 programme, the Polish Ministry for Science and Higher Education through grant No. 7150/E-338/SPUB/2017/1 and the National Science Centre, Poland (NCN) through grant No. 2017/25/N/NZ1/00861. Special thanks goes to dr hab. n. med. Magdalena Ulatowska-Białas for enabling histopathological examinations.

REFERENCES

[1] B. Stewart *et al.*, *World Health Organisation*, ISBN: 978-92-832-0429-9 (2014).
[2] P. Moskal, B. Jasińska, E.Ł. Stępień, S.D. Bass, *Nature Rev. Phys.* **1**, 527 (2019).
[3] R. Fodde *et al.*, *Nature Rev. Cancer* **1**, 55 (2001).
[4] S. Niedźwiedzki *et al.*, *Acta Phys. Pol. B* **48**, 1567 (2017).
[5] P. Moskal *et al.*, US Patent 9851456 (2017), PL 227658 (2013).
[6] P. Moskal *et al.*, *Phys. Med. Biol.* **64**, 055017 (2019).
[7] P. Moskal *et al.*, *Phys. Med. Biol.* **61**, 2025 (2016).
[8] P. Moskal *et al.*, *Nucl. Med. Rev. Suppl. C* **15**, 81 (2012).
[9] B. Jasińska *et al.*, *Acta Phys. Pol. B* **48**, 1737 (2017).
[10] E. Kubicz *et al.*, *Nukleonika* **60**, 749 (2015).
[11] S.J. Tao, *J. Chem. Phys.* **56**, 5499 (1972).
[12] T. Goworek *et al.*, *Chem. Phys. Lett.* **272**, 91 (1997).
[13] T. Goworek *et al.*, *Chem. Phys.* **230**, 305 (1998).
[14] M. Eldrup *et al.*, *Chem. Phys.* **63**, 51 (1981).
[15] B. Jasińska *et al.*, *Acta Phys. Pol. A* **132**, 1556 (2017).
[16] A. Watson, P. Collins, *Digest. Dis.* **29**, 222 (2011).
[17] T. Levin *et al.*, *Ann. Intern. Med.* **145**, 880 (2006).
[18] K. Dulski *et al.*, *Hyperfine Interact.* **239**, 40 (2018).
[19] K. Dulski *et al.*, *Acta Phys. Pol. A* **132**, 1637 (2017).